

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
SALAMA) Atty. Dkt. **7014-120**
)
Appl. No. **National Stage of**)
PCT/DE2004/002297) Examiner: n/a
)
Filed: herewith) Group Art Unit: n/a

For: **Pharmaceutical composition comprising oxoplatin, the salts and derivatives thereof**

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please amend the above-identified application as set forth below.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 5 of this paper.

Remarks begin on page 11 of this paper.

Amendments to the Specification:

On page 1, between line 5 and 6, directly after the title, please insert the following paragraph:

-- This is the U.S. national stage of International application PCT/DE2004/002297, filed October 13, 2004 designating the United States and claiming priority to European application EP03090343.9, filed October 13, 2003 and U.S. provisional application 60/512,083, filed October 20, 2003. --

On page 1, between lines 8 and 9, please insert:

-- Field of the Invention --.

On page 1, between lines 16 and 17, please insert:

-- Background of the Invention --

On page 4, between lines 3 and 4, please insert:

-- Summary of the Invention --

On pages 4, please amend the paragraph starting on line 4 as follows:

-- Said object according to the invention is accomplished by the present invention by means of a kit comprising *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV) (*cis*-oxoplatinum, oxoplatin), particularly salts thereof, and, physically separated therefrom, a base material of a pharmaceutical agent selected from the group comprising a tablet, a capsule, a coated tablet, a suppository, an ointment, a cream, a solution for infusion and/or injection, and optionally information relating to contacting or combining the

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contents of the kit, said base materials being selected in such a way that, following contacting or combining the *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV) with the base material,

- the capsule comprises oxoplatin : silicon dioxide : mannitol or magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10;
- the tablet comprises *cis*-oxoplatin : lactose : corn starch : poly(O-carboxymethyl)starch sodium salt : calcium hydrogen phosphate $\times 2\text{H}_2\text{O}$: cellulose powder : magnesium stearate at a ratio of 10 to 500 : 20 to 150 : 1 to 10 : 1 to 10 : 1 to 10 : 0.1 to 7; or
- the tablet alternatively comprises *cis*-oxoplatin : silicon dioxide : magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10;
- the cream comprises *cis*-oxoplatin : benzyl alcohol : cetyl stearyl alcohol : Macrogol stearate 1000 : isopropyl palmitate : glycerol : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 0.1 to 7 : 1 to 10 : 0.1 to 7 : 0.1 to 7 : 0.2 to 8 : 0.2 to 8 : 20 to 60;
- the ointment comprises *cis*-oxoplatin : propylene glycol : Macrogol stearate 1000 : cetyl stearyl alcohol : vaseline at a ratio of 2 to 20 : 5 to 40 : 0.1 to 7 : 1 to 10 : 25 to 400;
- the gel comprises *cis*-oxoplatin : hydroxyethylcellulose : ~~chlorocresol~~ chlorocresol : sodium hydroxide : sodium hydrogen phosphate dihydrate : water at a ratio of 2 to 20 : 100 to 600 : 5 to 40 : 0.1 to 7 : 20 to 60 : 3,000 to 50,000;
- the suppository comprises *cis*-oxoplatin : silicon dioxide : hardened fat at a ratio of 0.1 to 10 : 0.1 to 10 : 30 to 300; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose : corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : highly dispersed silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 700 to 4,000 : 200 to 600 : 10 to 1000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 10; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose $\times 1\text{H}_2\text{O}$: corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 1,000 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose $\times 1\text{H}_2\text{O}$: corn

- starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 1,000 : 1,500 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7:
- the solution for injection or infusion comprises *cis*-oxoplatin : benzyl alcohol : Polysorbate 80 : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 1 to 10 : 0.1 to 7 : 100 to 800 : 100 to 400; or
 - the solution for injection or infusion alternatively comprises *cis*-oxoplatin : mannitol : water at a ratio of 0.1 to 7 : 5 to 40 : 1 to 10. --

On page 12, please amend the paragraph starting on line 31 as follows:

- In still another preferred kit, the suppository, following contacting of *cis*-oxoplatin and base material, comprises 0.02 g of *cis*-oxoplatin, 0.02 g of silicon dioxide and 1.85 g of hardened fat; alternatively, the suppository comprises 20 mg of *cis*-oxoplatin, 1055, 40 mg of lactose, 170 mg of corn starch, 63.60 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide, and 0.5 mg of Polysorbate 80; alternatively, the suppository comprises 20 mg of *cis*-oxoplatin, 1350 mg of lactose \times 1H₂O, 170 mg of corn starch, 65 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide, and 0.5 mg of Polysorbate 80, or, alternatively, the suppository comprises 50 mg of *cis*-oxoplatin, 1450 mg of lactose \times 1H₂O, 170 mg of corn starch, 65 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide, and 0.5 mg of Polysorbate 80. --

On page 13, please amend the paragraph starting on line 21 as follows:

- The pharmaceutical agents according to the invention, which can be produced using said kit, are capable of binding directly to a DNA. The *cis*-platinum compounds according to the invention have an octahedral configuration. Consequently, *cis*-oxoplatin in the meaning of the invention can form both intra- and inter-strand DNA complexes. Due to the specific structure of *cis*-oxoplatin, in contrast to cisplatin, the compounds of the invention form multiple bonds with DNA strands. Owing to the inter-strand-crosslinker complexes and intra-strand-

crosslinker complexes, the compounds of the invention show advantageous specific cytostatic effects in anti-tumor therapy. The DNA adducts of the compounds according to the invention show higher charge of the platinum central atom and further have two additional ligands bound to this center. Owing to the octahedral configuration of the platinum(IV) complexes according to the invention, highly specific, relatively slow DNA binding is possible, which shows a more efficient effect compared to e.g. binding of cisplatin with DNA. Another advantage is that *cis*-oxoplatin at comparable concentrations - unlike cisplatin - does not inhibit proteases such as trypsin or ~~α -chymotrypsin~~ α -chymotrypsin. Potency and effectiveness of the inventive pharmaceutical agents comprising *cis*-oxo-platinum(IV) are largely independent of the form of application of the agents. The agents can be administered perorally, orally, rectally, subcutaneously, intramuscularly, intravenously and intraperitoneally. Compared to well-known *cis*-platinum compounds, the compounds of the invention are also advantageous in that the therapeutic effect of the compounds according to the invention lasts longer, and furthermore, the compounds of the invention are highly effective at various stages of tumor growth, and *cis*-oxoplatinum compounds show a longer lasting positive effect in therapy when compared to comparable *cis*-platinum compounds. These properties in solubility, pharmacogenetics, bioavailability, as well as degradation and ~~adsorption~~ absorption in the body allow more effective treatment of tumor diseases with the agents according to the invention as compared to well-known pharmaceutical agents comprising platinum. --

On page 37, between lines 16 and 17, please insert:

-- Description of Various and Preferred Embodiments of the Invention --.

On page 47, line 3 please delete "Claims" and insert therefore:

-- What is claimed is: --

Amendments to the Claims:

Please cancel claims 3 to 5 and 10 and add new claims 12 to 16 as forth hereinafter.

Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A kit, comprising *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV), particularly salts thereof, and, physically separated therefrom, a base material of a pharmaceutical agent selected from the group comprising a tablet, a capsule, a coated tablet, a suppository, an ointment, a cream, a solution for infusion and/or injection, and optionally information relating to contacting the contents of the kit, said base materials being selected in such a way that, following contacting the *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV) with the base material,

- the capsule comprises oxoplatin : silicon dioxide : mannitol or magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10;

- the tablet comprises *cis*-oxoplatin : lactose : corn starch : poly(O-carboxymethyl)starch sodium salt : calcium hydrogen phosphate $\times 2\text{H}_2\text{O}$: cellulose powder : magnesium stearate at a ratio of 10 to 500 : 20 to 150 : 1 to 10 : 1 to 10 : 1 to 10 : 1 to 10 : 0.1 to 7; or

- the tablet alternatively comprises *cis*-oxoplatin : silicon dioxide : magnesium stearate at a ratio of 0.1 to 10 : 0.1 to 10 : 0.1 to 10;

- the cream comprises *cis*-oxoplatin : benzyl alcohol : cetyl stearyl alcohol : Macrogol stearate 1000 : isopropyl palmitate : glycerol : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 0.1 to 7 : 1 to 10 : 0.1 to 7 : 0.1 to 7 : 0.2 to 8 : 0.2 to 8 : 20 to 60;

- the ointment comprises *cis*-oxoplatin : propylene glycol : Macrogol stearate 1000 : cetyl stearyl alcohol : vaseline at a ratio of 2 to 20 : 5 to 40 : 0.1 to 7 : 1 to 10 : 25 to 400;

- the gel comprises *cis*-oxoplatin : hydroxyethylcellulose : chloro-aerosol : sodium hydroxide : sodium hydrogen phosphate dihydrate : water at a ratio of 2 to 20 : 100 to 600 : 5 to 40 : 0.1 to 7 : 20 to 60 : 3,000 to 50,000;

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- the suppository comprises *cis*-oxoplatin : silicon dioxide : hardened fat at a ratio of 0.1 to 10 : 0.1 to 10 : 30 to 300; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose : corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : highly dispersed silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 700 to 4,000 : 200 to 600 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 10; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose \times 1H₂O : corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 100 : 1,000 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7; or
- the suppository alternatively comprises *cis*-oxoplatin : lactose \times 1H₂O : corn starch : adipic acid : sodium hydrogen carbonate : stearic acid : magnesium stearate : silicon dioxide : Polysorbate 80 at a ratio of 10 to 1,000 : 1,500 to 5,000 : 300 to 1,000 : 10 to 1,000 : 10 to 1,000 : 1 to 100 : 1 to 100 : 1 to 15 : 0.1 to 7;
- the solution for injection or infusion comprises *cis*-oxoplatin : benzyl alcohol : Polysorbate 80 : 70% sorbitol solution : water at a ratio of 0.2 to 8 : 1 to 10 : 0.1 to 7 : 100 to 800 : 100 to 400; or
- the solution for injection or infusion alternatively comprises *cis*-oxoplatin : mannitol : water at a ratio of 0.1 to 7 : 5 to 40 : 1 to 10.

2. (Currently Amended) The kit according to claim 1,
~~characterized in that~~ wherein
said kit is a chemotherapeutical kit.
3. (Cancelled)
4. (Currently Amended) A pharmaceutical agent ~~which can be produced by combining~~ comprising the components of the kit according to claim 1 ~~or 2~~.
5. (Currently Amended) The pharmaceutical agent according to claim 4,
~~characterized in that~~ wherein
the capsule additionally comprises silicon dioxide and mannitol or silicon dioxide and magnesium stearate and/or pharmaceutically acceptable vehicles, especially

siosomes, liposomes and/or nanocapsules.

6. ((Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the capsule comprises 50 mg of silicon dioxide, 50 mg of mannitol or 50 mg of magnesium stearate and 50 mg of oxoplatin, or, alternatively, 50 mg of *cis*-oxoplatin, 39.5 mg of lactose or 39 mg, 2.5 mg or 2 mg of corn starch, 2.5 mg of poly(O-carboxymethyl)starch sodium salt, 2.5 mg of calcium hydrogen phosphate $\times 2\text{H}_2\text{O}$, 2.5 mg of cellulose powder, and 0.5 mg of magnesium stearate, or, alternatively, 50mg of *cis*-oxoplatin, 50 mg of silicon dioxide and 50 mg of magnesium stearate.

7. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the capsule comprises 50 mg of silicon dioxide, 50 mg of mannitol or 50 mg of magnesium stearate and 50 mg of oxoplatin, or, alternatively, 50 mg of *cis*-oxoplatin, 39.5 mg of lactose or 39 mg, 2.5 mg or 2 mg of corn starch, 2.5 mg of poly(O-carboxymethyl)starch sodium salt, 2.5 mg of calcium hydrogen phosphate $\times 2\text{H}_2\text{O}$, 2.5 mg of cellulose powder and 0.5 mg of magnesium stearate, or, alternatively, 50mg of *cis*-oxoplatin, 50 mg of silicon dioxide and 50 mg of magnesium stearate.

8. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the cream comprises 50 mg of *cis*-oxoplatin, 20 mg of benzyl alcohol, 100 mg of cetyl stearyl alcohol, 25 mg of Macrogol stearate 1000, 20 mg of isopropyl palmitate, 40 mg of glycerol, 50 mg of sorbitol and 205 mg of water.

9. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the ointment comprises 50 mg of *cis*-oxoplatin, 120 mg of propylene glycol,

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5.5 mg of Macrogol stearate 1000, 22 mg of cetyl stearyl alcohol, and 851.5 mg of vaseline.

10. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the gel comprises 0.05 g of *cis*-oxoplatin, 1.8 g of hydroxyethylcellulose, 0.1 g of chloro-aerosol, 0.005 g of sodium hydroxide, 0.17 g of sodium hydrogen phosphate dihydrate, and 97.875 g of water.

11. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the suppository comprises 0.02 g of *cis*-oxoplatin, 0.02 g of silicon dioxide and 1.85 g of hardened fat, alternatively, that the suppository comprises 20 mg of *cis*-oxoplatin, 1055,40 mg of lactose, 170 mg of corn starch, 63.60 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide and 0.5 mg of Polysorbate 80, alternatively, that the suppository comprises 20 mg of *cis*-oxoplatin, 1350 mg of lactose \times 1H₂O, 170 mg of corn starch, 65 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide and 0.5 mg of Polysorbate 80, or, alternatively, that the suppository comprises 50 mg of *cis*-oxoplatin, 1450 mg of lactose \times 1H₂O, 170 mg of corn starch, 65 mg of adipic acid, 50 mg of sodium hydrogen carbonate, 5 mg of stearic acid, 4.5 mg of magnesium stearate, 3 mg of highly dispersed silicon dioxide and 0.5 mg of Polysorbate 80.

12. (Currently Amended) The pharmaceutical agent ~~according to any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the preparation of a 5 mg/ml injection or infusion solution comprises 5 mg of *cis*-oxoplatin, 9 mg of benzyl alcohol, 2 mg of Polysorbate 80, 650 mg of 70% sorbitol solution and 500 mg of water.

13. (Currently Amended) The pharmaceutical agent according to ~~any of the preceding claims,~~

~~characterized in that~~ claim 4, wherein

the tablet comprises 50 mg of *cis*-oxoplatin, 39.5 mg of lactose, 2.5 mg of corn starch, 2.5 mg of poly(O-carboxymethyl)starch sodium salt, 2.5 mg of calcium hydrogen phosphate $\times 2\text{H}_2\text{O}$, 2.5 mg of cellulose powder and 0.5 mg of magnesium stearate, or, alternatively, 50 mg of *cis*-oxoplatin, 50 mg of silicon dioxide and 50 mg of magnesium stearate.

14. (Cancelled)

15. (New) A method of producing a pharmaceutical agent for the treatment of tumors comprising combining components of the kit of claim 1, wherein said *cis*-diammoniumdichloro-*trans*-dihydroxoplatinum(IV) is incorporated in said base material prior to administration a patient.

16. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 4 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

17. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 6 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

18. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 7 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

19. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 8 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

20. (New) A method for the prophylaxis or therapy of a cancerous disease

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comprising administering the pharmaceutical agent of claim 9 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

21. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 10 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

22. (New) A method for the prophylaxis or therapy of a cancerous disease comprising administering the pharmaceutical agent of claim 11 to a person in need of such prophylaxis or therapy in a prophylactically or therapeutically effective amount.

Remarks

Claims 15 to 22 have been added and claims 3 and 14 are cancelled so that claims 1, 2, 4 to 13 and 15 to 22 are pending in this application of which claim 1 is in independent form. The above claim amendments and additions are made to eliminate improper multi-dependencies under U.S. practice so as to place the claims in form consistent with 37 CFR 1.75 (c) in order to insure examination of such claims. Minor omissions in the claims that were apparent from, among others, preceding sections of the respective claim, have also been rectified.

The amendments and additions are not "narrowing." The scope of the claims has not been reduced; no new limitations have been added and none are intended.

The disclosure has been amended to add appropriate headings. The disclosure has also been amended to correct a number of typographical or editorial errors (page 4, paragraph starting on line 4; page 12, paragraph starting on line 31 (editorial); page 13, paragraph starting on line 21). Applicant respectfully submits that a person skilled in the art reading the application as a whole would have understood to correct the typographical and, in particular the editorial error on page 12, according to the amendment submitted herewith. Thus, no new matter is believed to have been added.

Respectfully submitted,

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